REMARKS

I. Applicants thank the Examiner for the interview of 24 October 2007, where the above amended claims were advanced for discussion. The legal principles governing the prosecution as well as the science of neovascularization were discussed. It was agreed the claims above would overcome the novelty rejection, and Applicants would address the remaining §103 rejections.

II. In Item 2 of the Office Action, claims 1-3, 8, 27, 28, 30, 31, 43 and 45-47 were rejected under 35 U.S.C. 102(b) over WO99/26480.

The subject matter of non-rejected claim 33 is now incorporated in claim 1, thereby overcoming the rejection. Withdrawal thereof is requested respectfully.

III. On pages 3-10 of the Office Action, claims 1 and 29; claims 1 and 32; claims 1, 33 and 38; and claims 1, 33, 38-41 and 48-50 were rejected under 35 U.S.C. 103(a) over, in each rejection, WO99/26480, in view of Keshet et al. and Otani et al.; in view of the '826 patent; in view of the '107 patent; and in view of the '107 patent and the '826 patent, respectively. The Examiner detailed a number of deficiencies in WO99/26480 in constructing the rejections.

The rejections are traversed for the following reasons.

A. No Reasonable Expectation of Success, Teaching Away and Secondary Considerations Demonstrating Non-obviousness

Even if, arguendo, prima facie cases of obviousness were made, the unexpected observation of antiangiogenic activity of endostatin in the eye; the lack of a reasonable expectation of successfully obtaining antiangiogenic activity of endostatin in the eye, for that matter, in any tissue; and "secondary indicia or considerations," such as, long felt need, the prior

failed attempts of others and skepticism of others, rebut any such hypothetical prima facie cases of obviousness.

As discussed above and in previous submissions, Applicants pointed to failures of those in the art to demonstrate in vivo anti-angiogenic effects of endostatin. Additionally, applicants previously provided published documents that demonstrated, at the time of the claimed invention, those skilled in the art strongly doubted that endostatin was an effective antiangiogenic factor in vivo. Therefore at the time of the invention, one skilled in the art would not have had a reasonable expectation that endostatin could ameliorate or reduce the rate of ocular neovascularization in an individual. In fact, the publications and reports of record "teach away" from the use of endostatin to ameliorate or reduce the rate of ocular neovascularization in an individual.

The issue of the inability of endostatin to curtail cancer growth is probative. The first attempt to obtain in vivo use of endostatin was directed to inhibiting neovascularization associated with cancer. A number of research groups found that endostatin had no significant effect in cancer models. Thus, the prior failed attempts, including those by the first author of WO 99/26480, in the first indication for treatment with endostatin led those skilled in the art to conclude that endostatin was ineffective in blocking neovascularization. Hence, the long felt need of blocking neovascularization for treating disease remained unfulfilled.

Clearly, then, there was no reasonable expectation that endostatin would treat undesired neovascularization in any tissue in an individual, because of the failures to inhibit neovascularization involving cancer. The prior failed attempts by many resulted in skepticism in the art of endostatin having any in vivo use, e.g., see the Guo Declaration (submitted 22 May 2007), the Connelly Declaration (submitted 8 February 2006), and the Kaleko Declaration (submitted 8 February 2006), of record.

For example, in the Guo Declaration, Dr. Guo confirmed the knowledge of negative results of alleged in vivo endostatin activity in cancer. For example, Dr. Guo discussed a brief paragraph appearing in Science magazine; and the publication of Bachelot et al., an article which was co-authored by Leboulch, the first named author of WO99/26480, reporting no in vivo antiangiogenesis activity of endostatin in cancer. Endostatin research was not reproducible, not

consistent and not practicable. Dr. Guo referred to several other publications and reports attesting to the state of endostatin research, namely the lack of reproducibility of the original Folkman research and the skepticism that endostatin had any antiangiogenesis activity in a variety of models.

Thus, there was no reasonable expectation that endostatin would have any useful activity in vivo, and certainly no reasonable expectation that endostatin could treat ocular neovascularization in an individual. Moreover, the unexpectedness of the claimed invention and the relevant secondary indicia, for example, of prior failed attempts, skepticism in the art and an unmet long felt need, along with a clear teaching away in the art, would successfully rebut any case of obviousness. Accordingly, for those reasons, Applicants respectfully request that the §103 rejections be removed.

B. WO99/26480 Is Not Enabled

As discussed hereinabove and in the record, and herein incorporated by reference, WO99/26480 is not enabled as to the claimed invention and is therefore not an effective §103 publication.

As provided in *Impax v. Aventis* cited by the Examiner, if a reference is asserted against a patent, the patentee is entitled to present evidence of nonenablement, which would render that reference ineffective to support anticipation. The Impax court relied on *Amgen v. Hoechst Marion Roussel* (314 F.3d 1313 (Fed. Cir. 2003)) for that framework for such an analysis.

As noted in *In re Donohue*, 766 F.2d 531 (Fed. Cir. 1985),

> "*In re Wiggins*, 488 F.2d, 538, 179 USPQ 421 (CCPA 1973) and *In re Sheppard*, 339 F.2d 238, 144 USPQ 42 (CCPA 1964), do not support a contrary view. In those cases, the references were deemed insufficient, because they stated that attempts to prepare the claimed compounds were unsuccessful. Such failures by those skilled in the art (having possession of the information disclosed by the publication) are strong evidence that the disclosure of the publication was nonenabling."

Also, in *Fromson v. Advance Offset Plate*, 755 F.2d 1549 (Fed. Cir. 1985), the Federal Circuit stated,

> "The failed experiment reported in the prosecution history of the Mason patent renders that patent irrelevant as a prior art reference. As stated by Judge Learned Hand, "another's experiment, imperfect and never perfected will not serve either as an anticipation or as part of the prior art, for it has not served to enrich it.""

In the instant application, clear and convincing evidence of non-enablement of WO99/26480 has been presented. For example, several publications were made of record, each of which as a whole, demonstrate that endostatin was not believed to have an effective antiangiogenic activity in vivo.

That evidence clearly and convincingly demonstrates the lack of enablement and operability of WO99/26480. Hence, WO99/26480 is not an effective reference against the instant application. Accordingly, prima facie cases of obviousness have not been made, and for that additional reason, Applicants respectfully request the rejections be removed.

IV. Attached hereto is an Information Disclosure Statement referencing patent documents uncovered in the last few weeks. U.S. Pat. No. 7,122,181 is based on U.S. Ser. No. 10/245,050 filed 17 September 2002, published 1 May 2003 as U.S. Publ. No. 2003082159, which is a continuation-in-part of U.S. Ser. No. 10/025,264 filed 19 December 2001, published as U.S. Publ. No. 20020114783, which claims benefit to U.S. Ser. No. 60/256,701 filed 10 December 2000. There are two corresponding published PCT applications, both not designating the U.S., WO02/49677 published 27 June 2002 and WO2004/027033 published 1 April 2004.

CONCLUSION

Applicants submit that the pending claims are in condition for allowance and early indication of such is requested respectfully. Reexamination, reconsideration, withdrawal of the rejections and early indication of allowance are solicited earnestly. If any fees are found to be applicable, please charge any additional fees or make any credits to Deposit Account No. 02-1818.

Respectfully submitted,

BELL, BOYD & LLOYD LLC

BY

Dean H. Nakamura
Reg. No. 33,981
P.O. Box 1135
Chicago, Illinois 60690-1135
Phone: (202) 955-6851

Dated: 31 October 2007